



## Essential Oils and Seizures

### Anticonvulsant

Pharm Biol. 2017 Dec;55(1):63-67. Epub 2016 Sep 13.

#### **Antinociceptive and anticonvulsant effects of the monoterpene linalool oxide.**

##### **Abstract**

##### **CONTEXT:**

Linalool oxide (OXL) (a monoterpene) is found in the essential oils of certain aromatic plants, or it is derived from linalool. The motivation for this work is the lack of psychopharmacological studies on this substance.

##### **OBJECTIVE:**

To evaluate OXL's acute toxicity, along with its anticonvulsant and antinociceptive activities in male Swiss mice.

##### **MATERIAL AND METHODS:**

OXL (50, 100 and 150 mg/kg, i.p.) was investigated for acute toxicity and in the Rota-rod test. Antinociceptive activity was evaluated by the acetic acid-induced writhing test, and by formalin testing. Anticonvulsant effects were demonstrated by testing for pentylenetetrazol (PTZ)-induced seizures and by Maximum Electroshock headset (MES) test. OXL was administered to the animals intraperitoneally 30 min before for pharmacological tests.

##### **RESULTS:**

OXL showed an LD<sub>50</sub> of ~721 (681-765) mg/kg. In the Rota-rod test, it was observed that OXL caused no damage to the animal's motor coordination. OXL significantly reduced ( $p < .001$ ) the number of writhings. OXL also significantly decreased ( $p < .05$ ,  $p < .01$  or  $p < .001$ ) paw-licking time in the two phases of the formalin test. OXL significantly reduced ( $p < .01$  or  $p < .001$ ) the duration of tonic seizures in the MES test, and at the dose 150 mg/kg, significantly increased ( $p < .01$ ) the latency to first seizure in the PTZ test.

##### **CONCLUSION:**

The tested doses of OXL were safe, with no motor impairment, and show clear antinociceptive and anticonvulsant potential. Future investigations with this

monoterpene may lead to the development of a new molecule with even higher potency and selectivity.

Nat Prod Commun. 2014 Nov;9(11):1615-8.

**Anticonvulsant activity of Citrus aurantium blossom essential oil (neroli): involvement of the GABAergic system.**

Citrus aurantium L. blossoms are an important medicinal plant part in Iran and some other countries. It is used in traditional medicine as an antiseizure and anticonvulsant natural agent. Early in vitro research of the anticonvulsant activity of the blossom extracts were done but there has been no investigation focused on the blossom essential oil and its anticonvulsant activity. The anticonvulsant activity of the essential oil of C. aurantium blossoms (neroli) was investigated. The anticonvulsant activity of neroli was assessed in pentylenetetrazole (PTZ)-induced convulsion by i.v. and i.p. methods and maximal electroshock (MES) in mice, with diazepam as the standard drug. While mechanistic studies were conducted using flumazenil, a GABA A-benzodiazepine receptor complex site antagonist. Neroli produced protection against clonic by i.v administration of PTZ at 20 and 40 mg/kg, compared with protection with benzodiazepine. The mean onset and percentage protection against convulsion in neroli-treated mice were reduced by flumazenil. Intraperitoneal PTZ also decreased the latency of clonic seizure in the neroli (40 mg/kg) treated group. We also showed that neroli (20 and 40 mg/kg), exhibited inhibition of the tonic convulsion induced by MES and decreased the mortality rate. Neroli was analyzed by GC and GC-MS and twenty three constituents, representing 91.0 % of the chromatographical oil were identified. The major components of neroli were characterized as linalool (28.5%), linalyl acetate (19.6%), nerolidol (9.1%) E,E-farnesol (9.1%),  $\alpha$ -terpineol (4.9%) and limonene (4.6%) which might be responsible for the anticonvulsant activity. The results suggest that neroli possesses biologically active constituent(s) that have anticonvulsant activity which supports the ethnomedicinal claims of the use of the plant in the management of seizure.

J Ethnopharmacol. 2004 Oct;94(2-3):283-7.

**Anticonvulsant activity and chemical composition of Artemisia dracunculus L. essential oil.**

**Abstract**

Artemisia dracunculus L. (Asteraceae) has been used orally as an antiepileptic remedy in Iranian folkloric medicine. The anticonvulsant potential and composition of the essential oil obtained from the aerial parts of the plant were assessed in this study. The essential oil exerted dose- and time-dependent antiseizure activity in both maximal electroshock (MES) and pentylenetetrazole models of experimental seizures with ED50

values of 0.84 and 0.26 ml/kg, respectively. At some anticonvulsant doses, the essential oil produced sedation and motor impairment assessed by rotarod test. Gas chromatography (GC)/mass spectrometry (MS) analysis of the essential oil revealed the presence of trans-anethole (21.1%), alpha-trans-ocimene (20.6%), limonene (12.4%), alpha-pinene (5.1%), allo ocimene (4.8%), methyl eugenol (2.2%), beta-pinene (0.8%), alpha-terpinolene (0.5%), bornyl acetate (0.5%) and bicyclogermacrene (0.5%) as the main components. The observed anticonvulsant and sedative effects could be related to the presence of monoterpenoids in the essential oil.

J Ethnopharmacol. 1999 Feb;64(2):167-71.

**Evaluation of the anticonvulsant activity of the essential oil of *Eugenia caryophyllata* in male mice.**

**Abstract**

In this study, the effect of an essential oil of *Eugenia caryophyllata* (Myrtaceae), an antiepileptic remedy in Iranian folk medicine, against seizures induced by maximal electroshock (MES) or pentylenetetrazole (PTZ) in male mice was studied. The essential oil exhibited anticonvulsant activity against tonic seizures induced by MES. Although it was not effective against clonic convulsions induced by intraperitoneal administration of PTZ, the seizure threshold which was determined by an increase in the dose of intravenously infused PTZ required to induce clonus, was elevated by the essential oil. In addition, at some anticonvulsant doses, the essential oil produced motor impairment on the rotarod.

Epilepsy Res Treat. 2013;2013:532657. doi: 10.1155/2013/532657. Epub 2013 Jun 2.

**Increased seizure latency and decreased severity of pentylenetetrazol-induced seizures in mice after essential oil administration.**

**Abstract**

The effect of pretreatment with essential oils (EOs) from eight aromatic plants on the seizure latency and severity of pentylenetetrazol- (PTZ-) induced seizures in mice was evaluated. Weight-dependent doses of *Rosmarinus officinalis*, *Ocimum basilicum*, *Mentha spicata*, *Mentha pulegium*, *Lavandula angustifolia*, *Mentha piperita*, *Origanum dictamnus*, and *Origanum vulgare*, isolated from the respective aromatic plants from NE Greece, were administered 60 minutes prior to intraperitoneal (i.p.) injection of a lethal dose of PTZ to eight respective groups of Balb-c mice. Control group received only one i.p. PTZ injection. Motor and behavioral activity of the animals after EOs administration, development of tonic-clonic seizures, seizure latency and severity, and percentage of survival after PTZ administration were determined for each group. All groups of mice treated with the EOs showed reduced activity and stability after the administration of the

oil, except for those treated with *O. vulgare* (100% mortality after the administration of the oil). After PTZ administration, mice from the different groups showed increased latency and reduced severity of seizures (ranging from simple twitches to complete seizures). Mice who had received *M. piperita* demonstrated no seizures and 100% survival. The different drastic component and its concentration could account for the diversity of anticonvulsant effects.

Naunyn Schmiedebergs Arch Pharmacol. 2010 May;381(5):415-26. doi: 10.1007/s00210-010-0494-9. Epub 2010 Mar 17.

**Comparative anticonvulsant activities of the essential oils (EOs) from *Cymbopogon winterianus* Jowitt and *Cymbopogon citratus* (DC) Stapf. in mice.**  
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#### **Author information**

#### **Abstract**

The fresh leaves of *Cymbopogon citratus* are a good source of an essential oil (EO) rich in citral, and its tea is largely used in the Brazilian folk medicine as a sedative. A similar source of EO is *Cymbopogon winterianus*, rich in citronellal. The literature presents more studies on the EO of *C. citratus* and their isolated bioactive components, but only a few are found on the EO of *C. winterianus*. The objective of the present study was then to study, in a comparative way, the effects of both EOs on three models of convulsions (pentylentetrazol, pilocarpine, and strychnine) and on the barbiturate-induced sleeping time on male Swiss mice. The animals (20-30 g) were acutely treated with 50, 100, and 200 mg kg<sup>-1</sup>, intraperitoneally, of each EO, and 30 min later, the test was initiated. The observed parameters were: latency to the first convulsion and latency to death in seconds. Furthermore, the in vitro effects of the EOs were also studied on myeloperoxidase (MPO; a biomarker for inflammation) and lactate dehydrogenase (LDH; an index of cytotoxicity) releases from human neutrophils. The EOs radical-scavenging activities were also evaluated by the 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay. The results showed that both EOs were more active on the pentylentetrazol-induced convulsion model, and *C. citratus* was even more efficient in increasing latency to the first convulsion and latency to death. Both parameters were potentiated in the presence of a lower dose of diazepam (reference drug) when associated to a lower dose of each EO (25 mg kg<sup>-1</sup>). Besides, their anticonvulsant effects were blocked by flumazenil, a known benzodiazepine antagonist. This effect was somewhat lower on the pilocarpine-induced convulsion, and better effects were seen only with the EOs' higher doses (200 mg kg<sup>-1</sup>). A similar result was observed on the strychnine-induced convulsion model. Both EOs potentiated the barbiturate-induced sleeping time. However, *C. citratus* was more efficient. Interestingly, both EOs completely blocked the MPO release from human neutrophils

and showed no cytotoxic effect on the LDH release from human neutrophils. On the other hand, only a very low or no effect on the DPPH assay was observed with *C. winterianus* and *C. citratus*, respectively, indicating that the radical scavenging activity did not play a role on the EOs' effects. We conclude that the mechanism of action of the anticonvulsant effect of the EOs studied is, at least in part, dependent upon the GABAergic neurotransmission. In addition, their effects on inflammatory biomarkers can also contribute to their central nervous system activity.

Z Naturforsch C. 2009 Jan-Feb;64(1-2):1-5.

### **Evaluation of the anticonvulsant activity of terpinen-4-ol.**

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#### **Author information**

#### **Abstract**

Terpinen-4-ol is a monoterpenoid alcohol and component of the essential oils of several aromatic plants. Similarly to terpinen-4-ol, other monoterpenoid alcohols have shown anticonvulsant activity in convulsion animal models. The present study aimed to investigate the anticonvulsant activity of terpinen-4-ol. Treatment of mice with terpinen-4-ol (200 mg/kg) caused a significant decrease in the spontaneous motor activity at 30, 60 and 120 min after administration. Terpinen-4-ol (100 and 200 mg/kg) produced a significant dose-dependent increase in the duration of sleeping in mice. Pretreatment of mice with terpinen-4-ol at doses of 100, 200 and 300 mg/kg significantly increased the latency of pentylenetetrazole-induced convulsions. Terpinen-4-ol (200 and 300 mg/kg) also inhibited the induced seizures of picrotoxin. In another model, maximal electroshock seizure, terpinen-4-ol decreased the tonic hind convulsions percentage at the dose of 300 mg/kg. From the overall results we can conclude that terpinen-4-ol showed a depressant effect on the central nervous system and significant anticonvulsant activity.

#### **Convulsant / Increased Risk**

Pediatr Neurol. 2011 Oct;45(4):259-60. doi: 10.1016/j.pediatrneurol.2011.05.012.

### **Toxicity of *Salvia officinalis* in a newborn and a child: an alarming report.**

#### **Abstract**

Although it is widely believed that herbal products are beneficial to the health, some herbal products can result in serious adverse effects, such as epileptic seizures, especially in children who are particularly susceptible. Sage oil contains well-known convulsant substances such as thujone, camphor, and cineole in different proportions. We report 2 cases, those of a newborn and a toddler, who experienced generalized tonic-clonic seizures after accidental exposure to sage oil. No other causes of seizure

were detected by our clinical inquiries in either of the patients. The seizures occurred as an isolated event in the toddler, but in a repeated manner in the newborn; both patients experienced good outcomes. In any case of a first seizure of unexplained origin, the possibility of exposure to a herbal product should be kept in mind. Parents should be informed about the pros and cons of these untested remedies, which are presented as an alternative to conventional medicine.

Clin Toxicol. 1981 Dec;18(12):1485-98.

### **Toxicity of some essential plant oils. Clinical and experimental study.**

#### **Abstract**

Commercial preparations of essences of sage, hyssop, thuja, and cedar have caused human intoxication in eight cases, from which tonico-clonic convulsions were the major symptom. The experimental study of the toxic properties of commercialized essential oils of sage and hyssop has revealed that their convulsant action was of central nervous system origin in unanesthetized rats, as proven by electrocortical records. The toxicity of the hyssop oil seems to be more powerful than that of sage, since the dose limit from which the cortical events are only subclinical is 0.08 g/kg for hyssop oil and 0.3 g/kg for sage oil. Above 0.13 g/kg for hyssop oil and 0.50 g/kg for sage oil, the convulsions appeared and became lethal above 1.25 g/kg with hyssop oil and 3.2 g/kg with sage oil. The daily repeated injection of subclinical doses revealed the cumulative toxic effect of hyssop oil, since the same low dose induced electrocortical clonic seizures. The toxicity of each oil appeared to be related to the presence of terpenic ketones, camphor in sage commercial oil, camphor and thujone in sage Dalmatian oil, thujone in thuja and cedar oils, and pinocamphone in hyssop oil. The convulsant properties of camphor are well known. The neurotoxicity of thujone and pinocamphone is demonstrated in rats for the first time.

Rev Electroencephalogr Neurophysiol Clin. 1979 Jan-Mar;9(1):12-8.

### **[Experimental study of the toxic convulsant properties of commercial preparations of essences of sage and hyssop (author's transl)].**

#### **Abstract**

Commercial preparations of essences of sage and hyssop have caused poisoning of human beings and were found to possess a convulsant action of central origin in animals. The convulsant effect of hyssop essence appears to be more powerful than that of sage in non-anaesthetized rats. The dose limit, below which the cortical phenomena are subclinical, is 0.08 g/kg for hyssop, while above 0.13 g/kg convulsions appear and become lethal above 1.25 g/kg. The same doses for essence of sage are respectively 0.3, 0.5 and 3.2 g/kg. The neurotoxicity of hyssop appears to be related to the presence of two terpene ketones, pinocamphone and isopinocamphone, the former

of which has powerful convulsant properties, and is lethal at doses above 0.05 ml/kg. The toxicity of essence of sage is due to the presence of camphor which is well-known to possess convulsant properties.

J Neurol. 1999 Aug;246(8):667-70.

**Plant-induced seizures: reappearance of an old problem.**

**Abstract**

Several plant-derived essential oils have been known for over a century to have epileptogenic properties. We report three healthy patients, two adults and one child, who suffered from an isolated generalized tonic-clonic seizure and a generalized tonic status, respectively, related to the absorption of several of these oils for therapeutic purposes. No other cause of epilepsy was found, and outcome was good in the two adult cases, but the course has been less favorable in the child. A survey of the literature shows essential oils of 11 plants to be powerful convulsants (eucalyptus, fennel, hyssop, pennyroyal, rosemary, sage, savin, tansy, thuja, turpentine, and wormwood) due to their content of highly reactive monoterpene ketones, such as camphor, pinocamphone, thujone, cineole, pulegone, sabinylacetate, and fenchone. Our three cases strongly support the concept of plant-related toxic seizure. Nowadays the wide use of these compounds in certain unconventional medicines makes this severe complication again possible.

Epileptic Disord. 2011 Sep;13(3):345-7. doi: 10.1684/epd.2011.0451.

**Epileptic seizure induced by fennel essential oil.**

**Abstract**

An epileptic seizure is reported in a 38-year-old woman, known to be an epileptic patient. Although she was under antiepileptic treatment and had well-controlled epilepsy, she developed a typical generalised tonic-clonic seizure and remained unconscious for 45 minutes following ingestion of a number of cakes containing an unknown quantity of fennel essential oil. Involuntary diarrhoea accompanied her epileptic seizure. This reported case recalls the fact that fennel essential oil can induce seizures and that this oil should probably be avoided by patients with epilepsy. Labelling of products with fennel essential oil should refer to the risk of seizures, particularly for patients with epilepsy. An awareness programme should involve all stakeholders affected by this issue.

Epilepsy Behav. 2001 Dec;2(6):524-532.

**Herbal Medicines and Epilepsy: The Potential for Benefit and Adverse Effects.**

Spinella M.

**Abstract**

The widespread availability and use of herbal medicines raise the potential for adverse effects in the epilepsy population. Herbal sedatives (kava, valerian, chamomile, passion flower) may potentiate the effects of antiepileptic medications, increasing their sedative and cognitive effects. Despite some antiseizure effects in animal models, they should not be used in place of standard seizure medications because efficacy has not been established. Anecdotal, uncontrolled observations suggest that herbal stimulants containing ephedrine (ephedra or ma huang) and caffeine (cocoa, coffee, tea, maté, guarana, cola or kola) can exacerbate seizures in people with epilepsy, especially when taken in combination. Ginkgo and ginseng may also exacerbate seizures although the evidence for this is similarly anecdotal and uncertain. St. John's wort has the potential to alter medication pharmacokinetics and the seizure threshold. The essential oils of many plants contain epileptogenic compounds. There is mixed evidence for evening primrose and borage lowering the seizure threshold. Education of both health care providers and patients is the best way to avoid unintentional and unnecessary adverse reactions to herbal medicines.